
Clinical experience with combination disease-modifying antirheumatic drug therapy with cyclosporine

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ABSTRACT

Objectives

We previously reported on the clinical use of cyclosporine (Neoral®), alone or in combination with methotrexate (MTX), in the first 46 refractory rheumatoid arthritis (RA) patients treated at our centre between March 1996 and November 1997. Thirty of the 46 patients remained on cyclosporine at study completion (mean dose 2.98 mg/kg/day) with efficacy inferred by significant reductions in the prednisolone and MTX doses and creatinine maintained in an acceptable range. Early discontinuation was primarily related to non-serious side effects.

Methods

The 30 patients continuing cyclosporine were reviewed 12 months later in November 1998. Analysis included life-table techniques.

Results

21 of the original 46 patients (46%) continued at a mean dose of 2.59 mg/kg/day after a mean of 23.4 months. Nine patients discontinued cyclosporine during this 12-month period: 3 due to inactive disease, 2 due to hypertension, 2 due to elevated creatinine, and 1 due to mononeuritis multiplex secondary to rheumatoid vasculitis, and 1 due to inefficacy. Patients continuing cyclosporine had a shorter disease duration (9.85 versus 15.5 years [$P=0.05$]). The prednisolone dose decreased from a baseline value of 10.57 mg/day to 6.78 mg/day ($P=0.007$) and the MTX dose from 15.6 mg/week to 13.1 mg/week ($P=0.02$). The mean serum creatinine level increased from a baseline of 73.86 $\mu\text{mol/l}$ to 85.8 $\mu\text{mol/l}$ (16%). 21/30 patients on combination therapy with MTX showed no difference in discontinuation rates compared with those on cyclosporine alone. Life-table analysis showed a bimodal distribution with significantly increased cyclosporine discontinuation in the first 12 months (principally due to non-renal/hypertensive causes) versus the subsequent period.

Conclusion

This follow-up study indicates that the

use of cyclosporine in refractory RA allows a reduction in the prednisolone and MTX doses. Utilization is longer in earlier disease and is unaffected by combination with MTX. Renal function is maintained within an acceptable range. The bimodal discontinuation curve reflects early patient/physician concern about minor side effects, while renal/hypertension changes resulted in later discontinuation.

Introduction

Rheumatoid arthritis (RA) has an increased risk of significant morbidity and early mortality (1). Thus management requires knowledge of current treatment paradigms, particularly those involving disease-modifying antirheumatic drugs (DMARDs). Our approach, like that of many others, is to introduce DMARDs very early in the clinical course of diagnosed RA. Indeed, many patients are treated at the preliminary PISA (persisting inflammatory symmetrical arthritis) stage, even before RA has been definitely diagnosed. In patients deemed to have mild disease, drugs such as hydroxychloroquine or sulphasalazine are favoured, but if moderate-to-severe disease is present or predicted, then methotrexate (MTX) will be used. The decision with regard to the choice of agent at this level is often empirical, however, and based on both the patient's preference and the doctor's knowledge. The early introduction of combination therapies will occur if disease control is sub-optimal (2).

The recent availability of cyclosporine (Neoral®) in our country has allowed a change in our treatment algorithm for RA patients with severe disease. In this report we review the first 46 patients treated at our institution with cyclosporine both alone and in combination with MTX. Pharmaceutical regulations required us to use the medication in those patients with more severe disease, often with pre-existing significant damage and of long disease duration. At the onset of our treatment program, we had no personal ex-

perience of the frequency and extent of potential side effects with cyclosporine. Our experience with this drug, both alone and in combination with MTX, has provided useful clinical insights.

Life-table analysis of treatments

Over the last decade our group has used life-table analysis to assess the clinical utility of a number of DMARDs (3-5). Life-table analysis of drug discontinuation is principally a surrogate for both the efficacy and tolerance of that drug and represents a dynamic equilibrium between the two. The efficacy, as judged by drug continuation, reflects the perceptions and options of both the patient and physician.

Minor drug intolerance is not recorded on the life-table, and thus the nuances in dose modification and the encouragement of the patient by the physician to continue the drug despite non-serious side effects are subtle. Drug intolerance leading to discontinuation is judged according to known facts and concerns about the drug, and this in turn depends a great deal on the physician's experience with that agent. Thus, patients' concerns might be heightened when a new drug is provided, and minor side effects may not be acceptable if reassurance from the physician is not forthcoming. In turn, the physician may be very cautious when using an unfamiliar drug and is loathe to cause any lasting side effects if these seem evident even in the early stage. The patient and the doctor therefore come to an agreement about the continuation of a drug based on perceived benefits and the viability of other treatment options. The background state of the RA, the inflammatory activity, the extent of damage, and the psychological coping skills of the individual patient are all parameters that enter into this everyday clinical equation.

Life-table analysis of course provides information which traditional randomised controlled clinical trials cannot. Randomised trials have many limitations, including their short time frame and constraints on dosage and patient selection, and do not invariably apply to long-term effectiveness in everyday clinical practice. For instance, an analysis of 879 treatment episodes for RA using different

DMARDs in one community practice showed significantly better MTX retention rates compared with all other contemporary comparators (5). This finding was confirmed in a multi-practice group of 587 patients with RA (6). Further review at 12 years of 460 of these patients showed that 53% were still taking MTX (7). We have also shown that theoretical toxicity issues regarding combinations of DMARDs can be assessed in this same way. For instance, when MTX and sulphasalazine were first combined, there was concern that competition for folic acid might increase haematological toxicity and decrease the retention rates of the combination compared with either drug alone. Our life-table analysis showed that this was not in fact the case (3). Finally, life-table analyses will show an early learning-curve effect where drug retention decreases rapidly over the initial period as patients and doctors sort out their concerns about the medication. As experience is gained, the slope of the dropout rate more clearly reflects the genuine efficacy and tolerability of the agent.

With the above considerations in mind, we set out to apply these methods to the evaluation of cyclosporine in the first patients receiving this drug at our clinic.

Previous study - methods and results

We have previously reported on our first 21 months experience with 46 patients treated with cyclosporine (Neoral®) at Monash Medical Centre (8).

We reviewed the charts of all patients who commenced cyclosporine for the treatment of RA at our hospital between March 1, 1996 and November 30, 1997. Neoral became available in Australia for the treatment of RA on March 1, 1996. There were strict guidelines to follow for its prescription to be fully funded by the Australian Government Pharmaceutical Benefit Scheme, principally that patients had to have previously failed therapy with DMARDs, including MTX.

Of the 46 patients, 33 (72%) were female and 13 (28%) were male. Their average age was 54.8 years. Thirty of the 46 (65%) were still taking cyclosporine at the end of the study period, with a mean duration of therapy of 10.5 months

Table I. Side effects requiring drug cessation (n = number of events).

Side effects requiring drug cessation	n
Nausea, abdominal pain	5
High serum creatinine	4
Hypertension	4
Hirsutism	1
Lethargy	1
Panic attacks	1
Infection	1
Tremors	1
Headache	1
Pins and needles	1
Unknown	1

and a mean dosage of 2.94 mg/kg/day. Sixteen of the 46 (35%) patients did not tolerate cyclosporine, 3 due to inefficacy and 13 due to side effects. The mean duration of therapy at follow-up for the group that discontinued treatment was 5.9 months, and the mean dosage at the time of discontinuation was 2.46 mg/kg/day. There was a statistically significant difference in the duration of disease between those who continued on cyclosporine (mean duration 9.93 years) compared with those who did not (mean duration 15.73 years) ($P = 0.004$). Thirty-seven of the 46 (80%) patients were taking prednisolone at the commencement of cyclosporine therapy at a mean dosage of 10.36 mg/day. At the end of the study the mean dosage had decreased to 7.06 mg/day ($P < 0.0001$).

Thirty of the 46 (65%) patients were on combination therapy with MTX at the time of starting cyclosporine. The mean dose of MTX decreased from 15.08 mg/week at baseline to 13.67 mg/week ($P = 0.02$) at the conclusion of the study period. The mean cyclosporine dose of the patients on combination therapy (MTX and cyclosporine) was 2.8 mg/kg/day compared with 2.7 for those patients not on MTX. For the patients on combination therapy, the mean serum creatinine changed from 72.2 $\mu\text{l/l}$ to 80.60 $\mu\text{l/l}$ (an increase of 11.6%), compared with cyclosporine alone, which changed from 77.38 $\mu\text{mol/l}$ to 89.5 $\mu\text{mol/l}$ (an increase of 15.7%).

Current study and methods

The primary objective of this further 12-

month extension study was to determine the retention rate for cyclosporine alone compared with cyclosporine combined with MTX in the same group of RA patients, who were followed for another year until November 1998. The secondary objectives were: (1) to determine whether the reason for termination of the cyclosporine was lack of efficacy or toxicity, and (2) if the latter, to determine the nature of the toxicity.

Results

We reviewed the charts of the 30 patients who were still taking cyclosporine at the completion of the original study on November 30, 1997, for a further 12-month period to November 30, 1998. The retention rates for cyclosporine alone and for cyclosporine combined with MTX are shown in Figure 1.

During this follow-up period, 9 of the 30 patients discontinued the drug. There were 4 withdrawals from therapy due to side effects: 2 cases of uncontrolled hypertension and 2 patients with unacceptable rises in serum creatinine. One patient discontinued due to mononeuritis multiplex secondary to rheumatoid vasculitis, and one discontinued due to inefficacy. Three patients had their drug discontinued by their treating rheumatologist due to inactive disease (Table I). The mean dose of cyclosporine for those patients continuing the drug was 2.59 mg/kg/day (range 1.11-4.55) for a mean duration of 23.4 months (range 13-32.5) of therapy compared with 2.55 mg/kg/day (range 1.53-4.51) for all of those discontinuing at a mean duration of 8.51 months (range 0.25-28.5). The mean disease duration for those continuing the drug was 9.85 years (range 2-28) compared with 15.5 years (range 10-23) for those who discontinued the drug ($P = 0.001$).

The mean MTX dosage at the commencement of cyclosporine therapy in those continuing was 15.6 mg/week (range 5-25); this dosage had decreased to 13.1 mg/week (range 0-20) at study completion ($P = 0.02$) (Fig. 2). The mean prednisolone dosage changed from 10.57 mg per day (range 0-30) to 6.78 mg/day (range 0-15) ($P = 0.007$) (Fig. 3). The serum creatinine level in 19 of the patients continuing cyclosporine changed

Life-table analysis of Combination therapy (Cyclosporine and Methotrexate) versus Cyclosporine alone

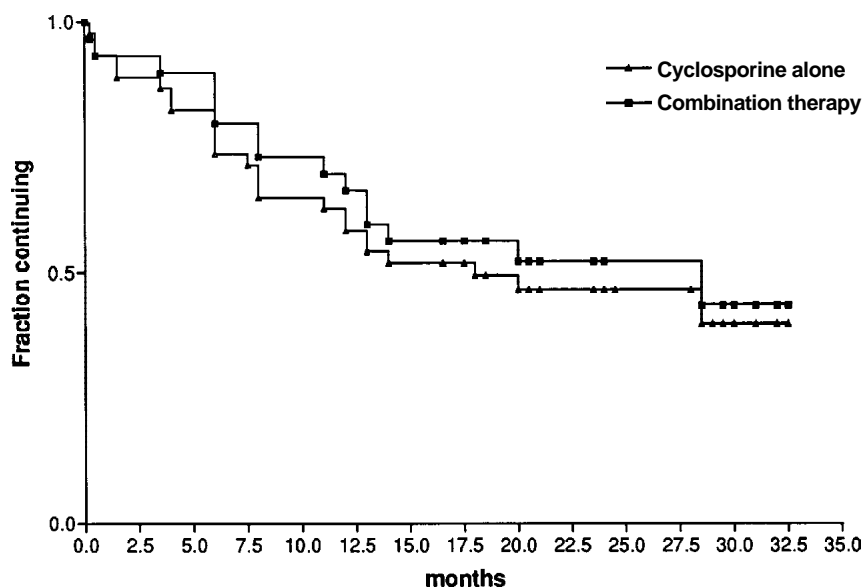


Fig. 1. Life-table analysis showing the fraction of all patients continuing on cyclosporine compared with the fraction of all patients continuing on combination therapy (cyclosporine and methotrexate).

from a baseline of 71.9 $\mu\text{mol/l}$ to 82.5 $\mu\text{mol/l}$, an increase of 14.7%. For those using combination therapy, there was an increase of 16% in the mean serum creatinine level from 73.86 $\mu\text{mol/l}$ to 85.8 $\mu\text{mol/l}$.

Discussion

We found cyclosporine (Neoral®), either used alone or with MTX, to be generally safe and well tolerated in this population of RA patients. No patient had severe or irreversible side effects and there

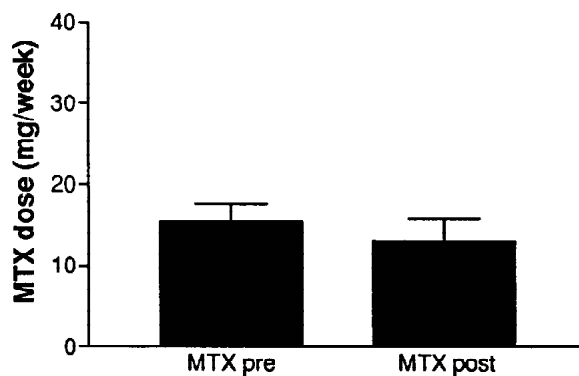


Fig. 2. Mean methotrexate (MTX) dose (mg/week) before and after cyclosporine treatment (mean \pm standard deviation) ($P = 0.02$).

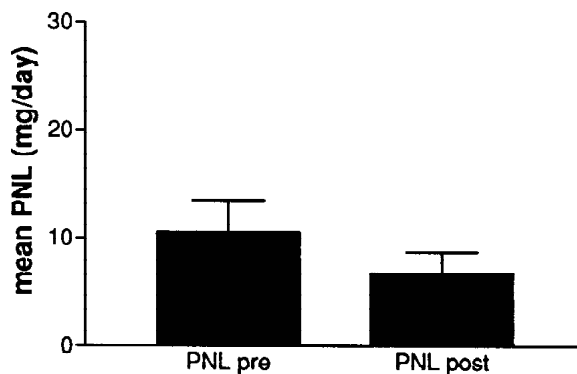


Fig. 3. Mean prednisolone (PNL) dose (mg/day) before and after cyclosporine treatment (mean \pm standard deviation) ($P = 0.007$).

was no evidence of toxicity induced by combination therapy. Despite this, we found a high discontinuation rate in the first 12 months of follow-up. This is shown by the bimodal shape of the life-table curve, with a significantly higher dropout rate in the first 12 months compared with the subsequent period. There appear to be several reasons for this.

The side effects leading to the discontinuation of the drug were influenced by the time intervals from the commencement of therapy. The causes of early drug discontinuation were usually patient-driven, with the most common cause being gastrointestinal upset and, to a lesser extent, anxiety, tremors, and hirsutism. In contrast to these early adverse events, we found that later withdrawal was often associated with more clinically important side effects, including elevations in serum creatinine and blood pressure. As our clinical experience with cyclosporine has grown, we have noted that many of these early adverse events, which had led to drug discontinuation in some patients, were often self-limiting or responded to a dose reduction. Hence, in patients currently commencing cyclosporine therapy we try to maintain the drug during the early stages despite minor side effects, by means of patient reassurance, explanation, and dosage modification.

The later side effects illustrate the need to maintain regular monitoring for the duration of cyclosporine therapy, in particular regular serum creatinine level and blood pressure monitoring. In several instances, we found the serum creatinine to rise unexpectedly after a period of stable measurements. We found that those patients who were most likely to develop renal or hypertensive problems had either a borderline blood pressure at baseline or were already receiving anti-hypertensives at the commencement of therapy. Some had high normal levels of serum creatinine at commencement. With stricter patient selection, these problems may be preventable.

Our data have also shown that those patients with a shorter disease duration were much more likely to remain on the drug than those with more prolonged disease. This may reflect underlying causes including age, concomitant illnesses, the use of other medications and

tolerability to additional medication, and the relative likelihood of having underlying blood pressure and renal abnormalities.

We found significant decreases in both the prednisolone and MTX doses in the group as a whole. These dose reductions represent a surrogate for drug efficacy. It suggests that the addition of cyclosporine in general improved disease control, thereby allowing for reductions in the dosage of MTX and prednisolone.

The results of our study show that, compared with the early controlled studies of cyclosporine in RA, the tolerated dose was much lower (9,10), but was similar to that in more recently published data (11,12). We postulate that this lower dose is better tolerated because there is a lower incidence of side effects, and hence patients and doctors are more likely to continue the drug. Based on our findings, we now recommend commencing cyclosporine therapy at a lower dose than previously - that is, at 2.0-2.5 mg/kg/day. We have learned other lessons from our experience in terms of patient selection which we believe will further improve the tolerability of cyclosporine in the future. In particular, it is important to select those patients with a short disease duration who have evidence of ongoing inflammatory changes that would be amenable to the recognised immunological effects of cyclosporine. Patients with blood pressure and serum creatinine in the low-to-mid-normal range rather than the high-normal range are, we believe, less likely to develop problems of high blood pressure and elevated serum creatinine with therapy. Although age *per se* does not necessarily determine tolerability, it does represent a risk factor for renal dysfunction and hypertension. We prefer to use cyclosporine in younger patients to reduce this risk.

Future directions

It is our current strategy to identify patients at risk of persisting RA and to introduce potent medications early. Our first drug of choice in such patients remains MTX, with the dose being increased to the maximum tolerated by the patient, usually between 20 mg and 30 mg once weekly orally or parenterally. If this does not bring the clinical features of RA under control, then a second agent

is added along the traditional lines of hydroxychloroquine/sulphasalazine. We now have the option of adding cyclosporine at an earlier stage. The patients most likely to benefit from cyclosporine appear to be those with a short disease duration, normal blood pressure and renal function, and low levels of anxiety and previous drug intolerance. As newer agents appear, the therapeutic algorithm will continue to evolve.

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